IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent application of: §
FAOUR, J. et al. §
§
Serial No.: 09/770,901 § Group Art Unit: 1617
Filed: January 26, 2001 § Examiner: Shaojia A. Jiang

Copy

For: Pharmaceutical compositions containing A COX-II inhibitor and a muscle relaxant

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on 01/02/02.

Rick Matos
Typed or printed name of person mailing paper

Signature of person mailing paper

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

(Duplicate)

DECLARATION UNDER RULE 37 C.F.R.§1.132

Further to the Office Action mailed September 28, 2001, the undersigned hereby declares as follows:

My name is Ethel C. Feleder. I reside in Luis María Campos 449, 2° A, Buenos Aires, Argentina.

I am knowledgeable in the area of Internal Medicine, Basic and Clinical Pharmacology and in particular in the area of the clinical evaluation of pharmaceutical formulations. My education, experience, publications and awards are summarized in my curriculum vitae, which is attached.

I am familiar with the subject matter of the invention disclosed and claimed in the above-identified patent application. In particular, I am familiar with conventional methods of analgesic therapy with individual drugs and with combinations of drugs.

With regard to the subject matter of claims 1-8, 40-45 and 49-54, I understand that the claims cover a pharmaceutical composition comprising a COX-II inhibitor and a muscle relaxant.

With regard to the subject matter of claims 10-38 and 46-48, I understand that the claims cover a pharmaceutical dosage form comprising a COX-II inhibitor and a muscle relaxant.

As a medical doctor, it is my belief that the claimed pharmaceutical compositions and dosage forms provide significant advantages over conventional analgesic compositions and dosage

forms used in pain therapy. In particular, the claimed pharmaceutical composition and dosage form provide an enhanced analgesic affect as compared to the administration of either agent alone. The exemplary formulation of rofecoxib and pridinol, the claimed composition and the claimed dosage form should also provide at least an additive analgesic effect.

Conventional analgesic therapy generally involves administration of a pharmaceutical composition containing one or two different analgesic drugs. However, not all combinations of analgesic drugs are more suitable, in terms of safety or efficacy, than the administration of a single product. Furthermore, the additivity of the analgesic effect of analgesic drugs cannot be predicted *a priori*. For example, M. R. Naidu et al. (*Pharmacotherapy* (1994), Mar-Apr., 14(2), pp. 173-177) report that the administration of ketorolac alone is superior in terms of analgesia to the combined administration of ibuprofen and paracetamol in the same or different dosage forms for the relief of postoperative. In addition, R. Dionne (*Compend. Contin. Educ. Dent.* (2000) July, 21(7), pp. 572-574 and 576-577) reports that the combination of an opioid with acetaminophen or aspirin does not provide greater analgesia but results in a higher incidence of side effects such as drowsiness and nausea. Moreover, S. Ilkjaer et al. (*Acta Anaesthesiol. Scand.* (2000), Aug., 44(7), pp. 873-877) report that the combination of ibuprofen with dextromethorphan provides no additive analgesic effect. Therefore, one of ordinary skill in the art would not necessarily *a priori* consider any and all combinations of analgesics to be suitable combinations or even consider that all analgesic combinations would result in additive analgesic effects.

The discovery or expectation of a synergistic analgesic effect from a combination of analgesic drugs or drug classes is also unpredictable. G. L. Wideman et al. (*Clin. Pharmacol. Ther.* (1999), Jan., 65(1), pp. 66-76) report that, when hydrocodone is administered with ibuprofen to a subject for the treatment of postoperative pain, an additive and not synergistic analgesic effect is found. R. A. Dionne (*J. Oral Maxillofac. Surg.* (1999), June, 57(6), pp. 673-678) reports that the combined administration of an nonsteroidal anti-inflammatory drug (NSAID), such as ibuprofen, and an orally effective opioid analgesic (such as oxycodone) to patients for the treatment of post-operative oral surgery provides an additive and not synergistic analgesic effect. S.M. Siddik et al. (*Reg. Anesth. Pain Med.* (2001), July-Aug., 26(4), pp. 310-315) report the results of a comparative study on the analgesic effects provided by morphine in combination with propacetamol and/or diclofenac. The combination of diclofenac and morphine

provides improved analgesia and resulted in reduced morphine demand, whereas the combination of propacetamol and morphine did not improve analgesia or reduce the demand for morphine significantly. In addition, the combination of diclofenac, propacetamol and morphine did not even provide an additive analgesic effect.

Therefore, it is truly unexpected that the combined administration of a COX-II inhibitor and a muscle relaxant provides an improved, additive or synergistic analgesic effect when administered to a subject as compared to the analgesic effect provided by the administration of either agent alone.

I further declare that the statements made herein, to my knowledge, are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Date: 12/20/2001

Ethel C. Feleder, M.D., PhD